Procter & Gamble

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***by* Email**

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Dr. William Stokes
Director, NICEATM
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RE: **Comments on the Background Review Document and Proposed ICCVAM Test Method Recommendations for Assessing the Dermal Corrosivity Potential of Chemicals**

Dear Dr. Stokes:

This provides comments on the Background Review Document (BRD) entitled "EPISKIN™, EpiDerm™, and Rat Skin Transcutaneous Electrical Resistance (TER) Methods: *In Vitro* Test Methods for Assessing the Dermal Corrosivity Potential of Chemicals" and the proposed Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) test methods recommendations on the use of these *in vitro* methods.

It is important to recognize the outstanding quality of the BRD. This document is well organized, comprehensive and clearly written. The authors and supervising management responsible for the BRD are to be congratulated for this exceptional effort.

Beyond this well-deserved recognition, we would like the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to consider the following comments:

- We recommend the validated, *in vitro* test methods described in the BRD and **Federal Register** announcement be accepted and advanced as definitive, absolute replacements of *in vivo* animal tests in the assessment of the corrosive potential of test materials.

- We suggest rewording or qualifying the BRD and related documents to avoid indirectly endorsing a test method/technology that is proprietary to one company and not otherwise commercially available.

The basis for these comments is provided in the following sections.

In the Federal Register announcement (**Federal Register**/Vol. 66, No. 189/Friday, September 28, 2001, pg. 49686) under *Proposed ICCVAM Recommendations*, it states: "Negative *in vitro* corrosivity responses shall be followed by *in vivo* dermal corrosion/irritation testing. (Note: The first animal used in the irritation/corrosivity assessment would be expected to identify any chemical corrosives that were false negatives in the *in vitro* test)", and " . . . as is appropriate for any *in vitro* assay, there is the opportunity for confirmatory testing if false positive results are indicated on a weight of evidence evaluation of supplemental information, such as pH, structure activity relationships (SAR), and other chemical and testing information". These recommendations appear in the BRD as well (2.0 Draft ICCVAM Test Recommendations).

Comment: We recommend the *in vitro* test methods presented in the BRD and **Federal Register** announcement should fully replace existing *in vivo* corrosivity tests for all products. As such, a positive or negative result obtained in one of the validated, *in vitro* assays for skin corrosivity should not require any additional animal testing. When data from such validated *in vitro* assays are used in combination with supplemental information, e.g., pH, SAR, etc., the potential skin corrosivity of a test product may be determined and used in any number of regulatory risk assessments.

The recommendation to conduct an *in vivo* corrosivity test to identify "false negatives" undermines the full validation process for this specific endpoint. Such a proposal implies that any result, positive or negative, obtained in the validated, *in vitro* tests would need to be verified using an animal test since *a priori* knowledge of a false positive or false negative presumably would not exist. Moreover, this approach reinforces the view that the *in vivo* animal test is the definitive assessment of skin corrosivity of a test product. Thus, the necessity of conducting any *in vitro* test is reduced to a dubious exercise of limited usefulness.

In fact, the validation studies as presented in the BRD demonstrate the reliability and relevance of the proposed *in vitro* test methods in relation to the animal [rabbit] model. Any result from the validated *in vitro* tests adequately predicts the response that would be expected *in vivo* based on the agreed to success criteria set forth in the validation studies. What is more, there would be little or no predictive value in exposing a single animal to test product as a confirmatory test given the inherent variability of the animal response. Thus, we believe the validated *in vitro* tests should fully replace the current animal test to predict the potential for skin corrosivity.

Throughout the BRD and **Federal Register** notice there are repeated references to EPISKIN™ and EpiDerm™, the commercial human skin models used in the corrosion

validation studies. As well, in the BRD, under ICCVAM Recommendations its states "When EpiDerm™ and EPISKIN™ are used as part of the integrated testing strategy for corrosivity/irritation . . .". Again, it is neither surprising nor overtly inappropriate that these human skin constructs are mentioned specifically.

Comment: We suggest the BRD and related documents be revised removing any reference to EPISKIN™ or, alternatively, include a qualifying statement regarding the current commercial *un*availability of this human skin model. This action would circumvent the indirect endorsement of a product that is available to a single company.

It is recognized that at the time of the validation studies both EPISKIN™ and EpiDerm™ were commercially available products. Since then, EPISKIN™ has become the property of a single company and is not being made available for use by other companies or individuals. As such, it is proprietary technology. Given this status, it would seem prudent that either the BRD and **Federal Register** notice be revised to remove any reference to this model or include a qualifying statement so as not to endorse or otherwise promote a product, which is unavailable.

Please contact me with any questions or comments.

Respectfully,
THE PROCTER & GAMBLE COMPANY

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Principle Scientist

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